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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,144	04/20/2001	Masayuki Tsuchiya	06501-076001	9796

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EXAMINER
SWOPE, SHERIDAN

ART UNIT	PAPER NUMBER
1652	11

DATE MAILED: 12/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/830,144	TSUCHIYA ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *12-26 and 28-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *20 April 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

DETAILED ACTION

Applicant's election with without traverse of Invention I, Claims 1-11 and 27 in Paper No. 10 is acknowledged. Claims 12-26 and 28-40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to non-elected Inventions, there being no allowable generic or linking claim. Claims 1-11 and 27 are hereby examined on their merits.

Specification-Objections

The abstract of the disclosure is objected to because it is a confusing, single, and run-on sentence. In addition, it does not convey the major invention of the application. Correction is required. See MPEP § 608.01(b).

The specification is objected to because it lacks a "Brief Description of the Drawings" section. Correction is required.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "the peptide fused with the TAB1" has no antecedent basis in Claim 1. Claim 5 should be amended to recite "a peptide fused with the TAB1" or to be dependent on Claim 2.

Claim 9 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the

invention. The phrase "the secondary antibody" has no antecedent basis in Claim 5. Claim 9 should be amended to recite "a secondary antibody".

Claims 10 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "...with, as an index..." is confusing. The term "index" is not defined by the claims, the specification does not provide a definition, and one of ordinary skill in the art would not be reasonably appraised of the meaning. It is suggested that Claim 10 be amended to recite "...binding is detected as a percent change in the expression level...".

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 and 27 are rejected under 35 U.S.C. 112, first paragraph. The specification, is enabling for a method of screening for compounds that inhibit the binding of the TAK1 set forth by SEQ ID NO: 2 with the TAB1 set forth by SEQ ID NO: 4. However, the specification does not reasonably provide enablement for methods of screening for compounds that inhibit the binding of any TAK1 with any TAB1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 1-11 and 27 are so broad as to encompass methods of screening for compounds that inhibit the binding of any TAK1 with any TAB1. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large

number TAK1 and TAB1 proteins broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired TAK1/TAB1 binding activity requires a knowledge of and guidance with regard to which amino acids in the proteins' sequences, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structures relate to the binding function. However, in this case the disclosure is limited to the TAK1 set forth by SEQ ID NO: 2 and the TAB1 set forth by SEQ ID NO: 4.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the Claims 1-11 and 27 which, encompasses methods of screening for compounds that inhibit the binding of any TAK1 with any TAB1. The specification does not support the broad scope of Claims 1-11 and 27 because the specification does not establish: (A) which TAB1 and TAK1 proteins are to be used in the binding assays; (B) regions of the TAK1 set forth by SEQ ID NO: 2 and the TAB1 set forth by SEQ ID NO: 4 which may be modified without effecting the binding activity; (C) the general tolerance of the binding activity to modification of the TAK1 set forth by SEQ ID NO: 2 and the

TAB1 set forth by SEQ ID NO: 4 and the extent of such tolerance; (D) a rational and predictable scheme for modifying any residues within the TAK1 set forth by SEQ ID NO: 2 and the TAB1 set forth by SEQ ID NO: 4 with an expectation of obtaining the desired biological function; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices of variant TAK1 and TAB1 proteins is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including methods of screening for compounds that inhibit the binding of any TAK1 with any TAB1. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 1-11 and 27 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to methods using genera of TAK1 and TAB1 molecules having binding activity with each other. The specification teaches the structure of only a single TAK1 molecule and a single TAB1 molecule which, are representative species of such genera. Moreover, the specification fails to describe any other representative species of TAK1 and TAB1

by any identifying characteristics or properties other than the functionality of binding with each other. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Matsuomoto et al, 1998. Matsuomoto teach a method for screening the ability of inhibitors of TFG-β signaling to inhibit TAK1/TAB1 interaction (col 5, lines 7-35).

Claims 1-9 are rejected under 35 U.S.C. 102(a) as being anticipated by Ono et al, 1999. Ono et al teach a method for screening substances that inhibit binding between TAK1 and TAB1 (Claim 1) wherein, the TAB1 or TAK1 are fused to another polypeptide (Claim 2), or wherein TAK1 or TAB1 are bound to a support (Claim 3), or wherein TAK1 or TAB1 are labeled and said label detected (Claim 4), or wherein TAK1 or TAB1 are detected by an antibody to TAK1 or TAB1 or by an antibody directed to the fused polypeptide (Claims 5, and 6, 9), or wherein TAK1 or TAB1 are detected by an antibody to TAK1 or TAB1 or by an antibody directed to the fused polypeptide followed by an secondary antibody to the primary antibody (Claims 7-9).

Therefore, Claims 1-9 are rejected under 35 U.S.C. 102(a) as being anticipated by Ono et al, 1999.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shibuya et al, 1996 (IDS) and Metzler et al, 1977 or Matsuomoto et al, 1998, either in view of Ausubel, 1996 (Claims 1-3), Palaparti et al, 1997 (Claim 4), Swope et al, 1994 (Claims 5-9), or Fields et al, 1989 (Claims 10 and 11). Shibuya et al (Fig 1) teaches that TAB1 and TAK1 interact but do not teach screening compounds for inhibition of said interaction. However, it is common practice in the art to screen for inhibitors of binding (Metzler et al,). Matsuomoto et al, also teach that TAB1 and TAK1 interact and teach methods for screening for compounds that inhibit TAB1/TAK1 binding (col 5, lines 31-35). Neither the combination of Shibuya et al and Metzler et al, nor Matsuomoto et al teach the screening for compounds that inhibit TAK1/TAB1 binding using methods wherein, the TAB1 or TAK1 are fused to another polypeptide, or TAK1 or TAB1 are bound to a support, or TAK1 or TAB1 are labeled and said label detected, or TAK1 or TAB1 are detected by an antibody to TAK1 or TAB1 or by an antibody directed to the fused polypeptide, or TAK1 or TAB1 are detected by an antibody to TAK1 or TAB1 or by an antibody directed to the fused polypeptide followed by an secondary antibody to the primary antibody.

However, these methods are common in the art. Prior reports teach (i) methods wherein, components of the binding reaction are fused to another polypeptide (Ausubel, 1996; Chapter 20.2); (ii) methods wherein, one of the components is linked to a support (Ausubel, 1996; Chapter 20.2); (iii) methods wherein the binding is detected using a primary antibody or a primary antibody and a labeled secondary antibody (Swope et al, 1994; Fig 1); (iv) methods wherein, a label is attached to a binding component and the label detected (Palaparti et al, 1997; Fig 4); methods wherein, binding is detected by changes in expression of β-galatosidase (Fields et al, 1989). It would have been obvious to a person of ordinary skill in the art to use the methods of Ausubel, Palaparti et al, Swope et al, and Fields et al, which are standard in the art, to screen for inhibitors of TAB1/TAK1 binding. The use of said methods to screen for inhibitors of TAK1/TAB1 binding is suggested by Shibuya et al, 1996 and Metzler et al, 1977 showing that TAK1 and TAB1 do interact and that screening for inhibitors of protein/protein interaction is standard procedure. Motivation to use the methods of Ausubel, Palaparti et al, Swope et al, and Fields et al, to test for inhibitors of binding between TAK1 and TAB1 is provided by the desire to identify said inhibitors which, may be useful as pharmaceutical agents. The expectation of success is high as, binding between TAK1 and TAB1 has been demonstrated and the methods of Ausubel, 1996, Palaparti et al, 1997, Swope et al, 1994, and Fields et al, 1989 are standard procedures that are extensions of the results of Shibuya et al, and Matsuomoto et al. Therefore, Claims 1-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shibuya et al, 1996 and Metzler et al, 1977 or Matsuomoto et al, 1998 both in view of Ausubel, 1996, Palaparti et al, 1997, Swope et al, 1994, and Fields et al, 1989.

Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shibuya et al, 1996 or Matsuomoto et al, 1998 in view of Shirakabe et al, 1997 (IDS). The teachings of Shibuya et al and Matsuomoto et al are described above. Neither Shibuya et al nor Matsuomoto et al teach a method for testing the ability of compounds that inhibit signal transduction through the inflammatory cytokines IL-1, TNF, IL-10, OR IL-6 to inhibit TAK1 and TAB1 binding. However, since TAK1 is activated by both TAB1 (Shibuya et al, 1996) and Il-1 (Shirakabe et al, 1997), it would have been obvious to a person of ordinary skill in the art to test whether inhibitors of Il-1 also inhibit TAK1/TAB1 binding by using the methods of Shibuya et al or Matsuomoto et al. Motivation to use the methods of Shibuya et al or Matsuomoto et al, to test the ability of compounds that inhibit signal transduction through IL-1, as well as other inflammatory cytokines, is provided by the desire to know whether TAK1/TAB1 binding mediates the action of inflammatory cytokines. Demonstrating such an effect would provide insights into possible pharmaceutical agents, for example, in the treatment of rheumatoid arthritis. The expectation of success is high as the method of Claim 27 is a simple extension of the methods of Shibuya et al and Matsuomoto et al. Therefore, Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Shibuya et al, 1996 or Matsuomoto et al, 1998 in view of Shirakabe et al, 1997.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 703-305-1696. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone

numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sheridan L. Swope, Ph.D.

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600